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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,586	03/01/2004	David G. Bermudes	872-A-US	9589

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EXAMINER	
VOGEL, NANCY S	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,586	BERMUDES ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 25-43 are pending in the case.

Any rejection of record in the previous action not addressed in this office action is withdrawn.

Specification

The specification remains objected to since the page numbers on the Table of Contents pages are separate and not consecutive with those of the remainder of the specification.

The following are new rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular tumor targeting Salmonella strains, and a method or using said strain, does not reasonably provide enablement for any tumor-targeting Salmonella strain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 25 covers a Salmonella strain which expresses F'pilus and produces filamentous bacteriophage and is capable of targeting tumors by intravenous administration. Dependent claims 26-36 and 40-43 recite that the strain is attenuated, that it delivers particular numbers of phage to tumors, and that it is present in a composition. Claims 37 recites the method for delivering filamentous bacteriophage to solid tumors using said Salmonella. Claims 38 and 39 recite kits comprising said Salmonella.

The nature of the invention is a composition comprising a tumor-targeting Salmonella bacterium containing a F' pilus and bacteriophage, and a method of delivering bacteriophage to solid tumors.

An analysis of the prior art

Regarding the use of bacteria as DNA delivery systems to mammalian cells, in order for such systems for be successful, the bacteria must first enter the cell and then escape from the vacuole to the cytosol. Movement from the vacuole to the cytosol is unpredictable because in many instances the bacteria are lysed by the host cell's defense system and any plasmids carried by the bacterial are degraded preventing

expression of heterologous nucleotide sequences. At best it would appear that only a few cells, if any, may be transformed with DNA carried by a bacterial vehicle as Grillot-Courvalin (Nature Biotechnology, 1998, 16:862-866) suggest that "direct introduction of DNA from bacteria to mammalian cells has been reported in very few instances" (page 865, discussion). Grillot-Courvalin support such observations by reporting that "factors such as entry route may have an effect" on DNA delivery. Grillot-Courvalin go on to report that a mouse dendritic cell line, which can internalize bacteria via micropinocytosis, did not express incoming DNA at 24 hours post-transfer. Grillot-Courvalin suggest that this failure could reflect rapid degradation of the invading bacteria by this cell type. It would appear that use of bacteria as DNA delivery vehicles is not very efficient in other cell lines as well as Grillot-Couvalin have reported that *E. coli* carrying a nucleotide sequence encoding the green fluorescent protein are only able to transform 0.3-1% of a transfected macrophage cell line. (see paragraph bridging pages 864-865). These observations are corroborated by Dietrich et al. (Nature Biotechnology, 1998, 16:181-185) who report that only about 0.03% of macrophages infected with a mutated form of *Listeria monocytogenes* express a green fluorescent protein reporter gene (page 183, column 2). Dietrich et al. also suggest that expression of a heterologous nucleotide sequence is not stable over time by observing a gradual loss of fluorescence over time. See page 183 at bottom of column 2. Dietrich report that the low efficiency of expression of GFP as compared to the number of macrophages infected may be due to the fact that only some of the attenuated bacteria infecting the host cells survive the antimicrobial milieu inside the phagosome and are

able to escape into the host cell cytosol, whereas the others are totally digested, including the plasmid DNA, and that not all *Listeriae* being taken up reach the host cell cytosol as an intact viable entity, but the plasmid DNA is still released into this compartment (see page 184 at top of column 2). Therefore, there is ample evidence in the prior art that the delivery of heterologous genes to eukaryotic cells via bacterial vectors is unpredictable and far from routine. Furthermore, the instant claims are drawn to tumor-targeting bacteria, which encompasses strains which preferably enter and survive in tumor cells as compared to normal cells.

Therefore, the state of the art as evidenced above suggests that use of bacteria as a vehicle for transferring heterologous nucleotide sequences to eukaryotic cells of an animal is undeveloped, inefficient, and unpredictable. The studies recited above demonstrate that only low efficiency of reporter gene expression occurs in cell line in vitro and only contemplate that bacteria could be used to transfer heterologous DNA sequences to the cells of an organism.

The relative skill of those in the art of recombinant DNA techniques and microbiology is high. The relative skill of those in the art of gene therapy and treatment of solid tumors using gene therapy is low.

The area of the invention is unpredictable. As discussed above, the method of gene therapy in general, and the use of bacteria as delivery systems to eukaryotic cells in vivo in particular, is highly complex and unpredictable and the skilled artisan at the time of the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the

effectiveness of a potential new delivery system, such as tumor-targeted bacteria containing a bacteriophage, cannot be predicted in the absence of in vivo testing. Furthermore, since the application does not clearly set forth methods for obtaining the property of tumor-targeting, which appears to depend on such unpredictable areas as bacterial adhesion to specific cells, ie tumor cells as opposed to normal cells, and survivability of said bacteria in tumor cells as opposed to bacterial death in normal cells, it would be quite unpredictable whether any particular Salmonella strain, with any particular genotype, would successfully target tumors as opposed to normal cells, including any normal cell target of Salmonella.

The present specification provides little direction or guidance to support the claimed invention. In particular it is noted that is it not clear what causes any tumor-targeting of the Salmonella strains in Example 6 of the specification. It is not clear if such targeting was selected in some undisclosed manner. The basis for the tumor targeting in the Salmonella used is not disclosed; thus it is unclear if one could readily generate such tumor targeting in other Salmonella strains or serotypes, unless it is an inherent property of all Salmonella.

Working Examples An example is disclosed wherein particular Salmonella expressing F'pilus are infected with a phagemid in which the gene of interest is green fluorescent protein (GFP) and are used to infect mammalian M2 cells. Expression of GFP is shown. Another example discloses injecting mice containing melanoma tumors with particular Salmonella that are expressing F' pilus and are infected with filamentous

phage M13KO7. Tumor and liver homogenates and supernatants are compared for the presence of bacteria and the presence of phage.

The quantity of experimentation necessary to carry out the claimed invention is high since the skilled artisan could not rely on the prior art of the present specification to teach how to use the claimed method. In order to demonstrate how to use the method to target solid tumors using tumor-targeting Salmonella strains, one of skill in the art would have to determine if a gene of interest encoded by a bacteriophage and delivered by a bacteria is delivered efficiently and preferentially to the targeted tumor type. One must determine if the bacterial composition would survive and bacteria would reach the targeted tumors efficiently and specifically, and in sufficient number to achieve a therapeutic effect, rather than being targeted by the immune system to some degree, despite their attenuated pathogenicity. One would have to determine how to make Salmonella strains which specifically target tumor cells, and which do not infect or attach to normal cells. Since neither the prior art nor the specification provides the answers to all of these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make the claimed strains and kits, and use the claimed method comprising administering tumor targeting

Salmonella strains other than those shown in the specification to specifically deliver filamentous phage to tumor cells, in Example 6.

Claims 25-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 1 is drawn to a Salmonella strain having the F'pilus and which produces filamentous bacteriophage and is tumor-targeting by intravenous administration.

The specification has disclosed multiple properties encompassed by the tumor-targeting definition at page 5 of the specification which includes serum resistance, facultative anaerobiasis, susceptibility to the hosts defensive capabilities to limit replication I normal tissues but not within tumors where the host defensive capabilities may be impaired, attenuation of virulence whereby susceptibility to the host defenses may be increased and the bacteria is tolerated by the host but does not limit intratumoral replication, invasive capacity towards tumor cells, motility to aid in permeation throughout the tumor, antibiotic sensitivity, and low reversion rats of phenotypes. Claims 25-43 are genus claims in terms of Salmonella strains which are

tumor targeting, kits encompassing said Salmonella, and a method of delivering filamentous phage to a tumor using said Salmonella strains. The disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the tumor-targeting Salmonella based on the teachings of the specification. While the specification provides an example of a strain in Example 6 which appears to deliver filamentous phage to tumor cells in greater amounts than to normal cells, there is no disclosure of which modifications of Salmonella could be made which result in such tumor targeting. Therefore, the specification does not describe the genus of tumor-targeting Salmonella in such full, clear, concise and exact terms so as to indicate that Application had possession of the claimed bacteria and method at the time of filing the present application. Thus, the written description requirement has not been satisfied.

Vas-Cath V. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed structure of the encompassed genus of tumor targeting Salmonella , and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere

statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Col. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the particular tumor targeting Salmonella of Example 6, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25, 26, 40-43 and by dependence, claims 27-39 are vague and indefinite in the recitation of "...capable of..." , since this phrase refers to a latent ability, and it is unknown whether the ability is expressed or observed in the invention.

Response to Arguments

Applicant's arguments with respect to claims 25-43 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, Ph.D.
PATENT EXAMINER